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Review

Rett syndrome: A coming of age

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Abstract. Rett syndrome (RTT) was first recognized in the late 1950s by Andreas Rett in Vienna and Bengt Hagberg in Uppsala. Hagberg, following a meeting with Rett, decided to call the disorder Rett syndrome in the landmark paper which appeared in the Annals of Neurology in 1983. That report led to the worldwide recognition of this relatively young and unique neurodevelopmental disorder, the concerted effort to establish its epidemiology, etiology, and natural history, and the establishment of clinical criteria for its diagnosis. Our understanding of RTT progressed rapidly, in part due to the remarkable diagnostic advances in genetics linking RTT with variations in the methyl-CpG-binding protein 2 (*MECP2*) gene at Xq28. In 2003, the NIH funded a Natural History study of RTT and related disorders which provided critical cross-sectional and longitudinal data that resulted in the increased understanding of RTT, the development of better management strategies, and an increase in pharmaceutical and gene-based products designed to provide specific therapies. The FDA-approved oral agent trofinetide has been shown to provide incremental improvements in the core features of RTT. Two gene-based therapies are currently being assessed in clinical trials in Canada and the US. Additional treatment strategies are being assessed at the clinical and translational levels.

Keywords: Rett syndrome, *MECP2*, clinical criteria, natural history, treatment strategies

1. Introduction

Rett syndrome (RTT) is a relatively young disorder whose understanding progressed rapidly, in part due to the remarkable diagnostic advances in genetics. An FDA approved oral agent (trofinetide) has provided incremental improvements and two gene-based therapies are currently being assessed in clinical trials in Canada and the US. RTT was first recognized in the late 1950s by Andreas Rett in Vienna and Bengt Hagberg in Uppsala. While they did not discuss their initial observations, Rett reported his early findings in 1966 including the observation that blood ammonia levels were increased in some of his subjects [1]. However, this report in German was not widely read. Hagberg had not found the same ammonia elevations and questioned whether they were observing the same disorder. Subsequently he spoke with child neurology colleagues across Europe who noted that the initial ammonia level elevation reported by Rett was spurious and the two were likely observing the same disorder. Hagberg, therefore, decided to report his findings along with those of colleagues in France and Portugal [2]. Prior to publication, he and Rett intersected around 1980. Following this conversation, Hagberg felt that the disorder should be called Rett syndrome. The paper which appeared in the Annals of Neurology in 1983 [2] led to the worldwide recognition of this unique neurodevelopmental disorder.

In the United States, RTT was recognized in five individuals at that time, three in Washington, DC, one in Seattle, WA, and one in Houston, TX. Mary Coleman, a child neurologist in Washington, DC

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had attended a meeting in Paris where she learned of this diagnosis. Vanja Holm, a developmental pediatrician in Seattle was visiting her native Sweden where she also became aware of this diagnosis. These prior interactions with experts in Europe led both to recognize the diagnosis in their subjects. In Houston, where I was at the time, a girl with clinical features consistent with RTT and whose pediatrician had seen the paper of Hagberg et al., was referred to the child development clinic at Texas Children's Hospital where I was a consultant. These five individuals together created a firestorm of study in the US. Similar stories occurred elsewhere across the world leading to an explosion of interest and study of RTT.

Andreas Rett led the way in generating enthusiasm for understanding and managing RTT by hosting important international meetings in Vienna in 1984, 1986, and 1988. Each meeting led to increasing interest in the international community and resulted in important advances in the epidemiology, etiology, and natural history of this unique disorder. Foremost in this was the establishment of clinical criteria for the diagnosis of RTT [3]. Important points to remember for these criteria are that males were specifically excluded whereas microcephaly was included as criteria. These would both change over time. Reports of males with features consistent with RTT led to modification of the clinical criteria in 1988 to include both females and males [4]. More recently, a review of the literature revealed that more than one hundred males have been reported and an additional group of nearly ninety are under study (Percy et al., paper under review). In terms of microcephaly, this was removed as a criterion when subsequent data did not support this feature [5, 6].

Causality was also discussed with emphasis on a genetic basis linking it to the X chromosome given the appearance of RTT virtually exclusively in females [7, 8]. Finally, significant emphasis was placed on clinical management of the disorder including growth and nutrition, epilepsy, breathing irregularities, gastrointestinal issues, and orthopedic considerations including scoliosis, contractures, and bone health.

In terms of causality, several studies explored the X chromosome and gradually narrowed the area of interest to Xq28 [8, 9]. In 1999, Amir and colleagues identified methyl-CpG-binding protein (*MECP2*) gene as the causative agent [10]. The gene had been well known in the cancer literature but was not considered to be a top candidate for RTT [11, 12]. However, its role as producing a methyl-binding protein that could affect the activation or repression of other genes indicated that it is a critical element in the development of the CNS.

Following the identification of *MECP2* as the causal link, the clinical criteria were again modified by an international consensus panel in 2002 [13]. Microcephaly was removed as it had been established that about 20% of those affected had a head circumference in the normal range [6]. Efforts were also made to improve understanding of these criteria worldwide.

With continuing progress in the worldwide diagnosis of RTT, information on prevalence and incidence emerged. Prevalence ranged from 1 : 10,000 to 1 : 22,000 females, but the presence of a national database demonstrated clear superiority in overall accuracy [14, 15]. Data from the Australian RTT Database in 2006 revealed a prevalence of 0.88/10,000 females and a total incidence of 1.1/10,000 females through age 12 years [16]. Survival was 77.8% at age 25 years compared to virtually 100% in all females in Australia. A re-evaluation of incidence in Australia in 2011 supported the prior figure with an incidence of 1.1/10,000 by age 32 years [17].

Following the paper of Hagberg and colleagues, variant presentations were described differentiating classical (typical) RTT and variant (atypical) RTT. In addition, two distinctly different variants were noted: an early-onset seizure variant [18] and a variant with very early neurodevelopmental delay [19]. These last two were subsequently established as their own unique disorders. The early-onset seizure disorder was associated with variations in *CDKL5* [20] and called *CDKL5* Deficiency Disorder (CDD); the early developmental delay disorder was linked to *FOXG1* variants and called *FOXG1* Deficiency (FD) [21].

Further, a much smaller number of males with features similar, if not identical with RTT, was identified beginning in the 1980's and, following the association of *MECP2* with RTT, was shown to have *MECP2* variants [22]. These males expressed a much wider range of clinical involvement including early onset neonatal encephalopathy [23], a male RTT encephalopathy with some features of RTT, a RTT phenotype, and others primarily featuring only significant developmental delay. Males with features typical for RTT were found to have either somatic mosaicism [22] or Klinefelter syndrome (47XXY) wherein they have two X chromosomes, one having an *MECP2* variant [24–26]. In addition, an extra copy of *MECP2*, noted principally in males, presents with an equally severe neurodevelopmental disorder [27–32]. This disorder is termed the identification of the *MECP2* Duplication Syndrome (MDS).

The subsequent discussion of RTT is derived from information gleaned from the US Natural History Study (US NHS). The US NHS provides the most comprehensive cross-sectional and longitudinal data covering a period of sixteen years. Elements of this study are being continued under the Centers of Excellence clinics supported by the International Rett Syndrome Foundation.

2. Natural History of RTT

In 2003, the NIH funded several rare disease studies for the purpose of developing natural history (NH) data that would improve understanding of these disorders and lead to the development of more effective management through pharmaceutical or gene-based products. RTT and related disorders were among these initial NHS. The NHS yielded critical information regarding the progression of RTT over time, but also encouraged clinical trial development that resulted in the FDA-approved oral agent, trofinetide [33, 34], and the initiation of three gene therapy clinical trials (NCT05606614; NCT05898620; and NCT06152237). Although concluded in 2021, the RTT NHS data continue to generate key information.

During the sixteen years of activity in the NHS, the overall enrollment exceed eighteen hundred individuals including more than sixteen hundred females with RTT. Only thirty males who had *MECP2* variants were identified [22]. The remaining enrollees had CDD, FD, and MDS. Among those with RTT, 86% had classic RTT and 14% had atypical RTT.

The new data from the NHS led to further revision of the 2002 consensus criteria [35] to simplify the principal features (Table 1): **after a period of apparently normal development, a regression of speech and motor skills followed with the main criteria now limited to the four principal elements: partial or complete loss of speech and hand use, absent or abnormal gait, and the presence of stereotypic hand movements such as hand wringing, hand patting, or hand mouthing occurring together or apart.** The supportive criteria were no longer required for establishing classic RTT. For atypical RTT, two of the four main criteria and five of eleven supportive criteria were required following a period of regression. These criteria emphasize the notion that RTT is a clinical diagnosis based on distinct clinical criteria, independent of molecular findings. In parallel with this revision, the NHS database was analyzed using the 819 enrolled participants to validate these revised criteria [36].

It is essential to apply these criteria for diagnosis as *MECP2* variants do not occur in everyone meeting these clinical criteria. Further, *MECP2* variants are found in individuals who do not have RTT, particularly mothers who are completely normal or who have significant developmental delays but lack the clinical features of RTT [37]. In both instances, the clinical presentations are felt to result from significant skewing of X chromosome inactivation.

The diagnosis of RTT is being made earlier and earlier. That is, the median age of diagnosis decreased from >3.7 to 2.5 years during the NHS [38]. This changing age at diagnosis is related not only to a larger

Table 1
Rett Syndrome (RTT) Clinical criteria

Typical or Classic RTT	Atypical or Variant RTT
Regression followed by recovery or stabilization	Regression followed by recovery or stabilization
All main criteria and all exclusion criteria	2 of 4 main criteria and all exclusion criteria
Main criteria: Partial or complete loss of purposeful hand skills; partial or complete loss of spoken language; dyspraxic or absent gait; stereotypic hand movements	
Supportive criteria not required; often present	5 of 11 supportive criteria required
Supportive criteria: Breathing disturbances when awake; bruxism when awake; impaired sleep pattern; abnormal muscle tone; peripheral vasomotor disturbances; scoliosis/kyphosis; growth retardation; small, cold hands and/or feet; inappropriate laughing/screaming spells; diminished response to pain; intense eye gaze – eye pointing	
Exclusion criteria: traumatic brain injury, neurometabolic disease, or severe infection; very abnormal development in first six months of life	

Neul et al. Ann Neurol 2010;68 : 944–950.

number of previously identified older individuals enrolled at the outset, but also to increased attention to the key clinical features and the availability of genetic testing. Importantly, nearly 90% of RTT diagnoses are made by subspecialists (child neurologists, developmental pediatricians, or geneticists). The diagnosis among pediatricians was less (5.2%) [38]. Strategies for educating diagnosticians should include specific factors that account for delayed diagnosis. These include recognition that the period of infancy is not completely normal. These infants are actually "too good" in that they eat and sleep and rarely fuss. Further, an abnormal deceleration in the rate of head circumference increase may be noted as early as one and one-half months of life, indicating the importance of assessing this growth parameter at each primary care visit. Also, concerns of the parents or grandparents should be taken seriously. Later in infancy, delays in the acquisition of normal developmental milestones must receive greater attention rather than attributing these findings to normal variation.

A key feature of the NHS findings along with data from the North American RTT Database was that of longevity [39, 40]. Assessment of longevity for individuals in the US and Canada showed that 50% survival exceeded 50 years of age. These findings contrast sharply with the analysis of survival for the original group evaluated by Rett in Vienna in which survival past age 25 years was rare. Current survival appears to be at least double that described for this original group seen by Andreas Rett [41].

Subsequent analysis of NHS data reinforced this determination of prolonged survival [40]. Further, evidence for significant longevity in RTT underscores the need for attention to the long-term care of these women. Their parents may reach an age when they can no longer provide the full-time care required and others, including siblings or relatives may not be able to assist.

A recent assessment of healthcare needs revealed that the costs in the US for all health resource utilization was>$40,000/year including nearly 50% of this total for RTT-related medical costs alone [42]. The additional costs for group home or other chronic care facilities will increase this figure significantly. Thus, the need for effective therapies for RTT and similar neurodevelopmental disorders is demonstrable.

3. Clinical issues evaluated in the NHS

Three prominent features of RTT integral to the diagnostic criteria are developmental delay, hand function, and hand stereotypies. While early development appears normal in RTT, this may be more apparent than real. Delays in developmental skills in gross and fine motor functions and receptive and expressive communication have a quite typical pattern both in classic and atypical RTT with clear delays becoming obvious after six months of life [43]. Impairments of hand function are linked closely to *MECP2* genotypic abnormality [44]. Nevertheless, continued decline in hand function is evident through age eighteen. The milder variants have a steeper rate of decline than those associated with more significant variations. Hand stereotypies (HS) were more frequent and earlier in onset in those with classic RTT or more severely affected atypical RTT [45]. It is remarkable that HS remain relatively stable over time whereas hand function continues to decline.

Growth is also remarkably affected in those with RTT with prominent growth failure displaying a strong correlation with genotype, disease severity, and overall development [5, 6]. Height, weight, and head circumference are significantly affected with height rarely exceeding 150 cm, weight 45 kg, and head circumference being microcephalic or less than the 2nd percentile in >75%. RTT-specific growth charts (height, weight, body mass index, and head circumference) have been created allowing the comparison of growth patterns by genotype and phenotype. These charts are available through rettsyndrome.org. It is particularly important to recognize that poor growth is associated with worse developmental progress, greater disease severity, and specific phenotype-genotype correlations. Further, anthropometric measurements indicated a close correlation between arm and leg circumference, skinfold thickness, and muscle area measurements in females with classic and severe atypical RTT compared with mild atypical RTT, showing a significant reduction in normal growth patterns [46]. These growth patterns and anthropometric measures in females with RTT differ significantly from normal while demonstrating clear differences between classic and mild or severe atypical RTT. The use of these data as biologic markers in clinical trials could provide critical endpoints.

Key clinical comorbidities of RTT were assessed in the NHS including gastrointestinal dysfunction, epilepsy, breathing irregularities, scoliosis, sleep, behavior/anxiety, and sexual maturation.

The prevalence of common gastrointestinal and nutritional disorders related to age and methyl-CpG-binding protein 2 (*MECP2*) gene status revealed important information [47, 48]. Gastrointestinal dysmotility including constipation was present in 92%, chewing and swallowing difficulties in 81%, weight deficits or excess in 47%, growth deficits in 45%, low bone mineral content or fractures in 37%, and biliary tract disorders in 3%. Separately, the prevalence of vitamin D deficiency was associated inversely with 25-hydroxyvitamin D (25-(OH) D) levels and the consumption of dietary sources of vitamin D. The effect of anticonvulsants on bone health in those with RTT was also noted. Further, a separate study of biliary tract dysfunction noted a 4.4% prevalence of biliary tract disease [49]. Individuals with biliary tract dysfunction presented with abdominal pain (94%), irritability (88%), weight loss (64%), and vomiting (52%). Biliary dyskinesia, cholecystitis, and cholelithiasis were identified in 90% by cholescintigraphy.

Epilepsy had been reported previously in 50%–80% of individuals with RTT [50–52]. Early reports from the NHS study characterized the clinical spectrum of epilepsy in RTT, but a subsequent study noted a 90% life-time prevalence of epilepsy including the longitudinal course of epilepsy and the patterns of seizure onset and remission [53]. Daily seizures were uncommon in RTT, the point prevalence being about 3%, whereas prolonged remission was less common than in other causes of childhood onset epilepsy. Still, complete remission off anti-seizure medications is possible.

Breathing irregularities are common in RTT typically occurring predominantly during wakefulness [54]. Cross sectional and longitudinal characteristics of awake breathing abnormalities in RTT were

examined in the NHS revealing awake breathing dysfunction in >90%, even more than epilepsy. Strong correlations existed with function in general, quality of life, and risk for cardiac dysrhythmia.

Scoliosis was identified in most individuals (nearly 90%) with RTT, 12% requiring surgical correction [55]. These findings corroborated previous reports on scoliosis and provided understanding of co-morbidities, clinical severity, and relative risk reduction for specific variants. Further analysis confirmed these results, indicating that surgical correction had increased to 18% [56]. Importantly, parents and caregivers overwhelmingly approved of the outcomes after this surgical correction.

Sleep behavior was characterized in Rett (RTT) including sleep-disordered breathing, noting an increased prevalence of sleep issues, and providing justification for additional assessments and sleep medication. Interestingly, siblings of those with RTT also reported difficulties in some aspects of sleep [57].

RTT is a complex neurodevelopmental disorder with both internalizing (e.g., anxiety, social withdrawal) and externalizing (e.g., aggression, self-abuse) that were validated in the NHS [58]. Anxiety-like behavior and anxiolytic treatments were extremely common (77.5%) [59]. The use of anxiolytic agents including selective serotonin reuptake inhibitors (SSRIs) was associated with increased anxiety-like behaviors ($p < 0.001$), older age ($p < 0.001$), and mild MECP2 variants ($p = 0.002$). The SSRIs were deemed to provide significant relief.

Pubertal trajectories in females with RTT deviate from the general female population with early pubertal onset (precocious puberty) noted in >25% and delayed menarche, approximately six months later than the average age of 12.5 years in the US female population [60]. Other clinical issues relate to cardiac function [61] and urinary tract disease [62]. Prolonged QTc interval was present in nearly 20% of those with RTT, seemed to be more prominent with increasing age, and was associated with nonspecific T-wave changes which also increased with age. Inasmuch as 25% of deaths are sudden and unexpected, the role of cardiac dysfunction deserves strong attention. Individuals with RTT may also present with urological dysfunction including frequent urinary tract infections, kidney stones, and urine retention. As such, urinary tract function also requires regular surveillance.

RTT, CDD, FD, and MDD have similar clinical features but also display distinct differences in severity, regression, and seizures [63]. Individuals with CDD were the most severely affected and had the youngest age at seizure onset (2 months), whereas children with MDD had the oldest median age at seizure onset (64 months) and lowest severity scores. RTT and FD were intermediate in both features. Smaller head circumference correlated with increased severity in all disorders and earlier age at seizure onset in MDD. Developmental regression occurred in all RTT participants (median = 18 months) but in only 23 to 34% of the other disorders. Seizure occurrence was highest for CDD (96.2%) and lowest for RTT (47.5%).

4. Genotype/phenotype correlations

When analyzed group-wise, specific variants in *MECP2* are associated with important differences in clinical aspects of RTT [64–66]. For an individual with a given variant, this correlation may not pertain. Among the common mutations, R133C, R294X, R306C, and late carboxy-terminal (3') truncating variants are associated with milder features whereas R106W, R168X, R255X, and R270X typically yield more significant involvement. These differences include ambulation, hand use, and language, three principal diagnostic features of Rett syndrome. Regardless of variant type, overall clinical severity does increase with advancing age in all mutation groups.

One of the features felt to be responsible for these differences within each variant is X chromosome inactivation (XCI). The presence of skewed XCI patterns, whether moderate or greater in extent, was noted in 36% ($n = 45/125$) individuals with classic RTT [67]. This is significantly greater than moderate

or greater XCI skewing in typically developing individuals. In RTT, most affected females arise from *de novo* variants in the father. Similarly, the paternal allele appears to be inactivated preferentially, resulting in the skewing. This is contrasted with the preferential inactivation of the maternal allele in individuals with CDD [67].

Parental age has been associated with increased risk for occurrence in some neurodevelopmental disorders such as Down syndrome. However, a detailed analysis of parental age among individuals with RTT failed to find a relationship between parental age and increased incidence of RTT [68].

As noted earlier, less than 5% of individuals meeting clinical criteria for RTT lack an *MECP2* variation. Among twenty-two RTT females lacking an *MECP2* variation, assessment by whole-exome sequencing and copy number variation (CNV) analyses revealed that three were found to have previously undetected *MECP2* variants [69]. For the remaining nineteen, seventeen (89.5%) had likely pathogenic variants in other genes and/or CNVs (ten individuals or 52.6%).

Numerous reports have suggested that males with *MECP2* variants would not survive due to embryonic lethality. As noted above, more than one hundred males have been reported in numerous small series from the 1980's, well before the association of *MECP2* with RTT. In the US NHS, thirty males with *MECP2* variants were enrolled representing a quite broad array of phenotypes [22]. These included a severe neonatal encephalopathy with markedly reduced survival, a male RTT encephalopathy including males with some, but not all features of RTT, and males with significant cognitive impairment only. Two males had classic RTT and were found to have somatic mosaicism with one X chromosome having an *MECP2* variant. Upon reporting these findings, an additional group of nearly sixty males was identified, nearly 80% having a *de novo MECP2* variant and nearly 20% having somatic mosaicism and features consistent with classic RTT. An additional male had Klinefelter syndrome (47XXY). Previously, association of RTT with Klinefelter syndrome was reported by Vorsanova et al. [24, 25].

5. Consensus clinical management guidelines

To improve the overall care of individuals with RTT, it became evident that a clinical management guideline developed by an international consensus panel was key [70]. This guideline lists the primary care provider as the quarterback of the management team with a host of subspecialists, including gastroenterologists, developmental pediatricians, orthopedists, child neurologists, epileptologists, and relevant therapists, participating in the management plans. No peer-reviewed, consensus-based therapeutic guidance for care in RTT existed prior to this report. The complete outline of these guidelines is shown in Table 2. Among the important periodic recommendations are assessments of growth and nutrition, at least annual assessments of routine laboratory studies (complete blood count, metabolic profile, lipid profile, and vitamin D).

6. Clinical trial development

A goal of the NHS was to establish longitudinal data that would provide critical knowledge about the expected course of RTT, but also provide key measures outcome assessment. An important aspect is the impression gained by parents/caregivers regarding their top concerns for those affected by RTT or RTT-related disorder [71]. From a list of twenty-four options plus an open-entry category, the top five caregiver concerns for classic RTT were lack of effective communication (24.8%), seizures (10.5%), walking/balance issues (8.3%), lack of hand use (8.0%), and constipation (7.5%). All other concerns were less than 5%. Further, concerns varied with age, level of clinical severity, and specific *MECP2* variants, but these five remained among the most significant.

Table 2
Consensus Clinical Guideline Recommendations

Guidelines for integration of care across primary and subspecialty providers	
Primary care physician should be quarterback	Annual assessments at a minimum: review general health, medications, allergies
Evaluate growth parameters	Height, weight, head circumference, Tanner stage
Routine laboratory assessments	CBC, metabolic profile, lipid profile, vitamin D level; ECG to assess QTc
Parents and caregivers maintain health records notebook	Clinic visits, genetic test results, growth records, and immunizations
Subspecialists referrals as needed	Neurology, GI, Orthopedics, Sleep, Behavior, Endocrine, Nutritionist, Physical Therapy, Occupational Therapy, Speech Therapy
Recognize need for extra time: Issues are complex.	

Fu C et al., BMJ Paediatr Open. 2020;4:e000717. DOI:10.1136/bmjpo-2020-000717 [70].

Quality of life (QOL) was also assessed for those with RTT [72] and their parents/caregivers [73]. In RTT, severe clinical impairment related strongly to poor physical QOL, but greater motor function severity was associated with better psychosocial QOL. On the other hand, better motor function was associated with poorer psychosocial QOL, suggesting that, in clinical trials, improvements seen in motor function could have negative effects in behavior and mood [72].

Caregiver quality of life was also deemed essential to assess. In this case, physical component scores were superior to mental component scores, particularly at younger ages [73]. Still, it became clear that over time, as parents aged and had greater requirements for the care of their children, physical components tended to deteriorate. With the long-term survival potential for RTT, this is a critical public health consideration.

Extending the observation that RTT requires total caregiver attention and leads to potential difficulties throughout life, the Caregiver Burden Inventory, designed originally for Alzheimer disease, was modified to provide a similar assessment of the RTT caregiver, adding to the clinical trial outcome measures under consideration [74].

The Motor Behavior Assessment (MBA) tool had been in use for RTT since the early 1990s [75] and was utilized throughout the NHS. To establish the factor structure, internal consistency, and validity of this measure, data from 1,075 NHS participants were analyzed. This led to the revised MBA (R-MBA) consisting of a five-factor model: (1) motor dysfunction, (2) functional skills, (3) social skills, (4) aberrant behavior, and (5) respiratory behaviors [76]. Validation of the R-MBA is on-going to establish this as an effective outcome measure.

Most recently, the Rett Syndrome Caregiver Assessment of Symptom Severity (RCASS) represents a newly developed outcome measure [77]. The RCASS has strong exploratory and confirmatory factor analysis, reliability, and validity in a four-factor model. Importantly, convergent validity exists with the R-MBA, the CGI Scale (discussed below), and the RTT QOL. An evaluation of sensitivity and reliability is underway.

7. Clinical global impression anchors

RTT-specific anchors for the Clinical Global Impression (CGI) Scales were developed to provide high quality severity and improvement outcome measures, specific to the core symptoms of RTT [78]. The CGI-S scale is a global measure of severity and the CGI-I scale is a measure of improvement to a given agent. Both employ a 7-point Likert scale. The CGI-S scale is based on anchors specific for RTT across the spectrum of disability. The CGI-I scale represents various levels of improvement (levels 1–3) or worsening (levels 5–7) centered around No change (level 4). These have been used in several RTT clinical trials, one leading to FDA approval of trofinetide [33, 34].

8. Biomarkers

The lack of biomarkers of disease state, disease severity, or treatment response for RTT has been approached from a metabolomic and neurophysiological assessment. Using a non-targeted metabolomic approach, sixty-six significantly altered metabolites were identified which are grouped broadly into amino acid, nitrogen handling, and exogenous substance pathways. These pathways point to oxidative stress, mitochondrial dysfunction, and alterations in gut microflora, offering a basis for identifying disease severity biomarkers [79].

The neurophysiology protocol focused on both visual and auditory evoked responses (EPs) and quantitative EEG from resting/background recordings noting that EPs could provide unbiased assessment of disease staging and potentially aid in prognosis and response to therapy [80]. Quantitative EEG, centered on alpha/delta frequency ratios, also correlated with severity in RTT. Both measures provide potential biomarkers for clinical trials.

Evaluation of EPs across RTT, CDD, FD, and MDD found consistent abnormalities in all for both visual and auditory EPs [81]. These studies are being refined to validate the similarities and differences.

9. Clinical trial efforts

Two recent clinical trials have involved drugs designed specifically for RTT, both of which showed positive results in mouse models.

The first, sponsored by Neuren Pharmaceuticals and subsequently Acadia Pharmaceuticals, resulted in the successful phase 3 study of trofinetide, yielding significant improvement in the co-primary endpoint markers, RSBQ and CGI-I. The FDA granted approval for trofinetide in March 2023 [33, 34, 82, 83].

The second trial, sponsored by Anavex Life Sciences, showed promise for blarcamesine in initial phases in adults and children in the US, Europe, and Australia. Unfortunately, the pediatric trial (EXCELLENCE) in the UK, Canada, and Australia failed to show significance in the RSBQ, the primary outcome marker (Anavex.com/post/Anavex-life-sciences-provides-update-rett-syndrome-program).

Finally, an ongoing trial in Australia is evaluating a broad-spectrum cannabinoid (NTI164-Neurotech) in fourteen children.

Two gene trials are underway sponsored by Taysha Gene Therapies (Taysha Corporate Presentation-4/30/2024 and Neurogene [84]. Although both are in early phases, these trials offer the prospects for disease-altering effects.

Innovative studies are being assessed at the translational level. These include evaluations of possible roles for DNA [85] and RNA [86] editing and the reversal of XCI to activate the normal X chromosome in cells expressing the variant gene without adversely affecting the existing normally expressing cells [87].

10. Summation

RTT, first recognized more than sixty years ago by Andreas Rett in Austria [1] as well as by Bengt Hagberg in Sweden, receive international attention in 1983, when Hagberg and colleagues [2] presented the first widely read paper which identified this disorder as Rett syndrome. The subsequent years have seen international attention not only to RTT, but also to the related neurodevelopmental disorders *CDKL5* Deficiency Disorder, *FOXG1* Disorder, and *MECP2* Duplication Disorder.

In the US, the efforts of Congress and federal agencies at the FDA and NIH rapidly accelerated rare disease research. The natural history of RTT and its related disorders was explored, advancing our understanding of them, expanding clinical expertise, and creating of Centers of Excellence through the International Rett Syndrome Foundation. The long-term goal of specific treatments for RTT has been realized with FDA approval of trofinetide in 2023. While not a cure, this agent does offer the possibility of incremental improvement on the core features of RTT. Many lessons have emerged from the NHS including the overall satisfaction of improving the lives of all (affected individuals, parents, and caregivers) with RTT and related disorders. The progress to-date indicates that RTT has, indeed, come of age.

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Ethical approval

No human study was involved in the preparation of this report.

Conflict of interest

Alan Percy is a co-Editor-in-Chief of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review. He was previously involved in treatment trials for both trofinetide (Neuren and Acadia Pharmaceuticals) and blarcamesine (Anavex Life Sciences). He is a consultant for Acadia Pharmaceuticals, Taysha Gene Therapies, and Neurogene.

References

[1] A. Rett, On a unusual brain atrophy syndrome in hyperammonemia in childhood, *Wien Med Wochenschr* **116**(37) (1966), 723–726.

[2] B. Hagberg, J. Aicardi, K. Dias and O. Ramos, A progressive syndrome of autism, dementia, ataxia, and loss of purposeful hand use in girls: Rett's syndrome: report of 35 cases, *Ann Neurol* **14**(4) (1983), 471–479.

[3] B. Hagberg, F. Goutieres, F. Hanefeld, A. Rett, et al., Rett syndrome: criteria for inclusion and exclusion, *Brain Dev* **7**(3) (1985), 372–373.

[4] E. Trevathan and M.J. Adams, The epidemiology and public health significance of Rett syndrome, *J Child Neurol* **3**(Suppl) (1988), S17–S20.

[5] R.J. Schultz, D.G. Glaze, K.J. Motil, D.D. Armstrong, et al., The pattern of growth failure in Rett syndrome, *Am J Dis Child* **147**(6) (1993), 633–637.

[6] D.C. Tarquinio, K.J. Motil, W. Hou, H.S. Lee, et al., Growth failure and outcome in Rett syndrome: specific growth references, *Neurology* **79**(16) (2012), 1653–1661.

[7] C. Schanen and U. Francke, A severely affected male born into a Rett syndrome kindred supports X-linked inheritance and allows extension of the exclusion map, *Am J Hum Genet* **63**(1) (1998), 267–269.

[8] K.A. Ellison, C.P. Fill, J. Terwilliger, L.J. DeGennaro, et al., Examination of X chromosome markers in Rett syndrome: exclusion mapping with a novel variation on multilocus linkage analysis, *Am J Hum Genet* **50**(2) (1992), 278–287.
[9] N.C. Schanen, E.J. Dahle, F. Capozzoli, V.A. Holm, et al., A new Rett syndrome family consistent with X-linked inheritance expands the X chromosome exclusion map, *Am J Hum Genet* **61**(3) (1997), 634–641.
[10] R.E. Amir, I.B. Van den Veyver, M. Wan, C.Q. Tran, et al., Rett syndrome is caused by mutations in X-linked MECP2, encoding methyl-CpG-binding protein 2, *Nat Genet* **23**(2) (1999), 185–188.
[11] A. Bird, P. Tate, X. Nan, J. Campoy, et al., Studies of DNA methylation in animals, *J Cell Sci Suppl* 19 (1995), 37–39.
[12] A.P. Bird and A.P. Wolffe, Methylation-induced repression–belts, braces, and chromatin, *Cell* **99**(5) (1999), 451–454.
[13] B. Hagberg, F. Hanefeld, A. Percy and O. Skjeldal, An update on clinically applicable diagnostic criteria in Rett syndrome, Comments to Rett Syndrome Clinical Criteria Consensus Panel Satellite to European Paediatric Neurology Society Meeting, Baden Baden, Germany, 11 September 2001, *Eur J Paediatr Neurol* **6**(5) (2002), 293–297.
[14] C.A. Kozinetz, M.L. Skender, N. MacNaughton, M.J. Almes, et al., Epidemiology of Rett syndrome: a population-based registry, *Pediatrics* **91**(2) (1993), 445–450.
[15] C.A. Kozinetz, M.L. Skender, N.L. MacNaughton, D.J. del Junco, et al., Population-based registries using multidisciplinary reporters: a method for the study of pediatric neurologic disorders, *J Clin Epidemiol* **48**(8) (1995), 1069–1076.
[16] C.L. Laurvick, N. de Klerk, C. Bower, J. Christodoulou, et al., Rett syndrome in Australia: a review of the epidemiology, *J Pediatr* **148**(3) (2006a), 347–352.
[17] S. Fehr, A. Bebbington, N. Nassar, J. Downs, et al., Trends in the diagnosis of Rett syndrome in Australia, *Pediatr Res* **70**(3) (2011), 313–319.
[18] F. Hanefeld, The clinical pattern of the Rett syndrome, *Brain Dev* **7**(3) (1985), 320–325.
[19] S. Rolando, Rett syndrome: report of eight cases, *Brain Dev* **7**(3) (1985), 290–296.
[20] J. Tao, H. Van Esch, M. Hagedorn-Greiwe, K. Hoffmann, et al., Mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5/STK9) gene are associated with severe neurodevelopmental retardation, *Am J Hum Genet* **75**(6) (2004), 1149–1154.
[21] F. Ariani, G. Hayek, D. Rondinella, R. Artuso, et al., FOXG1 is responsible for the congenital variant of Rett syndrome, *Am J Hum Genet* **83**(1) (2008), 89–93.
[22] J.L. Neul, T.A. Benke, E.D. Marsh, S.A. Skinner, et al., The array of clinical phenotypes of males with mutations in Methyl-CpG binding protein 2, *Am J Med Genet B Neuropsychiatr Genet* **180**(1) (2019), 55–67.
[23] P. Kankirawatana, H. Leonard, C. Ellaway, J. Scurlock, et al., Early progressive encephalopathy in boys and MECP2 mutations, *Neurology* **67**(1) (2006), 164–166.
[24] S.G. Vorsanova, I.A. Demidova, V. Ulas, I.V. Soloviev, et al., Cytogenetic and molecular-cytogenetic investigation of Rett syndrome: analysis of 31 cases, *Neuroreport* **8**(1) (1996), 187–189.
[25] S.G. Vorsanova, I.A. Demidova, A.D. Kolotii, O.S. Kurinnaia, et al., Klinefelter syndrome mosaicism in boys with neurodevelopmental disorders: a cohort study and an extension of the hypothesis, *Mol Cytogenet* **15**(1) (2022), 8.
[26] J.S. Schwartzman, A. Bernardino, A. Nishimura, R.R. Gomes, et al., Rett syndrome in a boy with a 47,XXY karyotype confirmed by a rare mutation in the MECP2 gene, *NeuroPediatrics* **32**(3) (2001), 162–164.
[27] M.J. Friez, J.R. Jones, K. Clarkson, H. Lubs, et al., Recurrent infections, hypotonia, and mental retardation caused by duplication of MECP2 and adjacent region in Xq28. *Pediatrics* **118**(6) (2006), e1687–e1695.
[28] H. Van Esch, M. Bauters, J. Ignatius, M. Jansen, et al., Duplication of the MECP2 region is a frequent cause of severe mental retardation and progressive neurological symptoms in males, *Am J Hum Genet* **77**(3) (2005), 442–453.
[29] H. Van Esch, MECP2 Duplication Syndrome, *Mol Syndromol* **2**(3-5) (2012), 128–136.
[30] M.B. Ramocki, S.U. Peters, Y.J. Tavyev, F. Zhang, et al., Autism and other neuropsychiatric symptoms are prevalent in individuals with MeCP2 duplication syndrome, *Ann Neurol* **66**(6) (2009), 771–782.
[31] M.B. Ramocki, Y.J. Tavyev and S.U. Peters, The MECP2 duplication syndrome, *Am J Med Genet A* **152A**(5) (2010), 1079–1088.
[32] S.U. Peters, C. Fu, B. Suter, E. Marsh, et al., Characterizing the phenotypic effect of Xq28 duplication size in MECP2 duplication syndrome, *Clin Genet* **95**(5) (2019), 575–581.
[33] J.L. Neul, A.K. Percy, T.A. Benke, E.M. Berry-Kravis, et al., Trofinetide for the treatment of Rett syndrome: a randomized phase 3 study, *Nat Med* **29**(6) (2023), 1468–1475.
[34] J.L. Neul, A.K. Percy, T.A. Benke, E.M. Berry-Kravis, et al., Trofinetide Treatment Demonstrates a Benefit Over Placebo for the Ability to Communicate in Rett Syndrome, *Pediatr Neurol* **152** (2023), 63–72.
[35] J.L. Neul, W.E. Kaufmann, D.G. Glaze, J. Christodoulou, et al., Rett syndrome: revised diagnostic criteria and nomenclature, *Ann Neurol* **68**(6) (2010), 944–950.
[36] A.K. Percy, J.L. Neul, D.G. Glaze, K.J. Motil, et al., Rett syndrome diagnostic criteria: lessons from the Natural History Study, *Ann Neurol* **68**(6) (2010), 951–955.

[37] K. Augenstein, J.B. Lane, A. Horton, C. Schanen, et al., Variable phenotypic expression of a MECP2 mutation in a family, *J Neurodev Disord* **1**(4) (2009), 313.
[38] D.C. Tarquinio, W. Hou, J.L. Neul, J.B. Lane, et al., Age of diagnosis in Rett syndrome: patterns of recognition among diagnosticians and risk factors for late diagnosis, *Pediatr Neurol* **52**(6) (2015), 585–591 e2.
[39] R.S. Kirby, J.B. Lane, J. Childers, S.A. Skinner, et al., Longevity in Rett syndrome: analysis of the North American Database, *J Pediatr* **156**(1) (2010), 135–138 e1.
[40] D.C. Tarquinio, W. Hou, J.L. Neul, W.E. Kaufmann, et al., The Changing Face of Survival in Rett Syndrome and MECP2-Related Disorders, *Pediatr Neurol* **53**(5) (2015), 402–411.
[41] M. Freilinger, A. Bebbington, I. Lanator, N. De Klerk, et al., Survival with Rett syndrome: comparing Rett's original sample with data from the Australian Rett Syndrome Database, *Dev Med Child Neurol* **52**(10) (2010), 962–965.
[42] D. May, K. Kponee-Shovein, M. Mahendran, N. Downes, et al., Epidemiology and patient journey of Rett syndrome in the United States: a real-world evidence study, *BMC Neurol* **23**(1) (2023), 141.
[43] J.L. Neul, J.B. Lane, H.S. Lee, S. Geerts, et al., Developmental delay in Rett syndrome: data from the natural history study, *J Neurodev Disord* **6**(1) (2014), 20.
[44] J. Neul, T.A. Benke, E.D. Marsh, J.B. Lane, D.N. Lieberman, S.A. Skinner, D.G. Glaze, B. Suter, P.T. Heydemann, A.A. Beisang, S.M. Standridge, Ryther RCC, R.H. Haas, L.J. Edwards, A. Ananth and A.K. Percy, Distribution of hand function by age in individuals with Rett syndrome, *Ann Ch Neurol Soc* **1**(3) (2023), 228–238.
[45] J.L. Stallworth, M.E. Dy, C.B. Buchanan, C.F. Chen, et al., Hand stereotypies: Lessons from the Rett Syndrome Natural History Study, *Neurology* **92**(22) (2019), e2594–e2603.
[46] K.J. Motil, S. Geerts, F. Annese, J.L. Neul, et al., Anthropometric Measures Correspond with Functional Motor Outcomes in Females with Rett Syndrome, *J Pediatr* 244 (2022), 169–177 e3.
[47] K.J. Motil, R.J. Schultz, K. Browning, L. Trautwein, et al., Oropharyngeal dysfunction and gastroesophageal dysmotility are present in girls and women with Rett syndrome, *J Pediatr Gastroenterol Nutr* **29**(1) (1999), 31–37.
[48] K.J. Motil, E. Caeg, J.O. Barrish, S. Geerts, et al., Gastrointestinal and nutritional problems occur frequently throughout life in girls and women with Rett syndrome, *J Pediatr Gastroenterol Nutr* **55**(3) (2012), 292–298.
[49] K.J. Motil, J.B. Lane, J.O. Barrish, F. Annese, et al., Biliary Tract Disease in Girls and Young Women With Rett Syndrome, *J Pediatr Gastroenterol Nutr* **68**(6) (2019), 799–805.
[50] D.G. Glaze, J.D. Frost, Jr., H.Y. Zoghbi and A.K. Percy, Rett's syndrome. Correlation of electroencephalographic characteristics with clinical staging, *Arch Neurol* **44**(10) (1987), 1053–1056.
[51] D.G. Glaze, Neurophysiology of Rett syndrome, *J Child Neurol* **20**(9) (2005), 740–746.
[52] D.G. Glaze, A.K. Percy, S. Skinner, K.J. Motil, et al., Epilepsy and the natural history of Rett syndrome, *Neurology* **74**(11) (2010), 909–912.
[53] D.C. Tarquinio, W. Hou, A. Berg, W.E. Kaufmann, et al., Longitudinal course of epilepsy in Rett syndrome and related disorders, *Brain* **140**(2) (2017), 306–318.
[54] D.C. Tarquinio, W. Hou, J.L. Neul, G.K. Berkmen, et al., The course of awake breathing disturbances across the lifespan in Rett syndrome, *Brain Dev* **40**(7) (2018), 515–529.
[55] A.K. Percy, H.S. Lee, J.L. Neul, J.B. Lane, et al., Profiling scoliosis in Rett syndrome, *Pediatr Res* **67**(4) (2010), 435–439.
[56] J.T. Killian, J.B. Lane, H.S. Lee, S.A. Skinner, et al., Scoliosis in Rett Syndrome: Progression, Comorbidities, and Predictors, *Pediatr Neurol* **70** (2017), 20–25.
[57] O.J. Veatch, B.A. Malow, H.S. Lee, A. Knight, et al., Evaluating Sleep Disturbances in Children With Rare Genetic Neurodevelopmental Syndromes, *Pediatr Neurol* **123** (2021), 30–37.
[58] C.B. Buchanan, J.L. Stallworth, A.E. Scott, D.G. Glaze, et al., Behavioral profiles in Rett syndrome: Data from the natural history study, *Brain Dev* **41**(2) (2019), 123–134.
[59] C.B. Buchanan, J.L. Stallworth, A.E. Joy, R.E. Dixon, et al., Anxiety-like behavior and anxiolytic treatment in the Rett syndrome natural history study, *J Neurodev Disord* **14**(1) (2022), 31.
[60] J.T. Killian, J.B. Lane, G.R. Cutter, S.A. Skinner, et al., Pubertal development in Rett syndrome deviates from typical females, *Pediatr Neurol* **51**(6) (2014), 769–775.
[61] J.A. Herrera, C.S. Ward, M.R. Pitcher, A.K. Percy, et al., Treatment of cardiac arrhythmias in a mouse model of Rett syndrome with Na+-channel-blocking antiepileptic drugs, *Dis Model Mech* **8**(4) (2015), 363–371.
[62] C.S. Ward, T.W. Huang, J.A. Herrera, R.C. Samaco, et al., Loss of MeCP2 Causes Urological Dysfunction and Contributes to Death by Kidney Failure in Mouse Models of Rett Syndrome, *Plos One* **11**(11) (2016).
[63] C. Cutri-French, D. Armstrong, J. Saby, C. Gorman, et al., Comparison of Core Features in Four Developmental Encephalopathies in the Rett Natural History Study, *Ann Neurol* **88**(2) (2020), 396–406.
[64] J.L. Neul, P. Fang, J. Barrish, J. Lane, et al., Specific mutations in methyl-CpG-binding protein 2 confer different severity in Rett syndrome, *Neurology* **70**(16) (2008), 1313–1321.

[65] A. Bebbington, A. Anderson, D. Ravine, S. Fyfe, et al., Investigating genotype-phenotype relationships in Rett syndrome using an international data set, *Neurology* **70**(11) (2008), 868–875.
[66] V.A. Cuddapah, R.B. Pillai, K.V. Shekar, J.B. Lane, et al., Methyl-CpG-binding protein 2 (MECP2) mutation type is associated with disease severity in Rett syndrome, *J Med Genet* **51**(3) (2014), 152–158.
[67] X. Fang, K.M. Butler, F. Abidi, J. Gass, et al., Analysis of X-inactivation status in a Rett syndrome natural history study cohort, *Mol Genet Genomic Med* **10**(5) (2022), e1917.
[68] X. Fang, L.M. Baggett, R.C. Caylor, A.K. Percy, et al., Parental age effects and Rett syndrome, *Am J Med Genet A* **194**(2) (2024), 160–173.
[69] S.A. Sajan, S.N. Jhangiani, D.M. Muzny, R.A. Gibbs, et al., Enrichment of mutations in chromatin regulators in people with Rett syndrome lacking mutations in MECP2, *Genet Med* **19**(1) (2017), 13–19.
[70] C. Fu, D. Armstrong, E. Marsh, D. Lieberman, et al., Consensus guidelines on managing Rett syndrome across the lifespan, *BMJ Paediatr Open* **4**(1) (2020), e000717.
[71] J.L. Neul, T.A. Benke, E.D. Marsh, B. Suter, et al., Top caregiver concerns in Rett syndrome and related disorders: data from the US natural history study, *J Neurodev Disord* **15**(1) (2023), 33.
[72] J.B. Lane, H.S. Lee, L.W. Smith, P. Cheng, et al., Clinical severity and quality of life in children and adolescents with Rett syndrome, *Neurology* **77**(20) (2011), 1812–1818.
[73] J.T. Killian, Jr., J.B. Lane, H.S. Lee, J.H. Pelham, et al., Caretaker Quality of Life in Rett Syndrome: Disorder Features and Psychological Predictors, *Pediatr Neurol* **58** (2016), 67–74.
[74] J.B. Lane, A.R. Salter, N.E. Jones, G. Cutter, et al., Assessment of Caregiver Inventory for Rett Syndrome, *J Autism Dev Disord* **47**(4) (2017), 1102–1112.
[75] P.M. FitzGerald, J. Jankovic, D.G. Glaze, R. Schultz, et al., Extrapyramidal involvement in Rett's syndrome, *Neurology* **40**(2) (1990), 293–295.
[76] M. Raspa, C.M. Bann, A. Gwaltney, T.A. Benke, et al., A Psychometric Evaluation of the Motor-Behavioral Assessment Scale for Use as an Outcome Measure in Rett Syndrome Clinical Trials, *Am J Intellect Dev Disabil* **125**(6) (2020), 493–509.
[77] M. Raspa, A. Gwaltney, C. Bann, J. von Hehn, et al., Psychometric Assessment of the Rett Syndrome Caregiver Assessment of Symptom Severity (RCASS), *J Autism Dev Disord* 2024.
[78] J.L. Neul, D.G. Glaze, A.K. Percy, T. Feyma, et al., Improving Treatment Trial Outcomes for Rett Syndrome: The Development of Rett-specific Anchors for the Clinical Global Impression Scale, *J Child Neurol* **30**(13) (2015), 1743–1748.
[79] J.L. Neul, S.A. Skinner, F. Annese, J. Lane, et al., Metabolic Signatures Differentiate Rett Syndrome From Unaffected Siblings, *Front Integr Neurosci* **14** (2020), 7.
[80] J.N. Saby, T.A. Benke, S.U. Peters, S.M. Standridge, et al., Multisite Study of Evoked Potentials in Rett Syndrome, *Ann Neurol* 2021.
[81] J.N. Saby, S.U. Peters, T.A. Benke, S.M. Standridge, et al., Comparison of evoked potentials across four related developmental encephalopathies, *J Neurodev Disord* **15**(1) (2023), 10.
[82] D.G. Glaze, J.L. Neul, W.E. Kaufmann, E. Berry-Kravis, et al., Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome, *Neurology* **92**(16) (2019), e1912–e1925.
[83] J.L. Neul, A.K. Percy, T.A. Benke, E.M. Berry-Kravis, et al., Design and outcome measures of LAVENDER, a phase 3 study of trofinetide for Rett syndrome, *Contemp Clin Trials* **114** (2022), 106704.
[84] B. Suter, D. Lieberman, T. Benke, J. Neul, et al., Preliminary Results from the Ph1/Ph2 Study of NGN-401, a Novel Regulated Gene Therapy for Rett Syndrome, 2024.
[85] N. Panayotis, Y. Ehinger, M.S. Felix and J.C. Roux, State-of-the-art therapies for Rett syndrome, *Dev Med Child Neurol* **65**(2) (2023), 162–170.
[86] J.R. Sinnamon, M.E. Jacobson, J.F. Yung, J.R. Fisk, et al., Targeted RNA editing in brainstem alleviates respiratory dysfunction in a mouse model of Rett syndrome, *Proc Natl Acad Sci U S A* **119**(33) (2022), e2206053119.
[87] N.B. Grimm and J.T. Lee, Selective Xi reactivation and alternative methods to restore MECP2 function in Rett syndrome, *Trends Genet* **38**(9) (2022), 920–943.